National Center for Emerging and Zoonotic Infectious Diseases

Epidemiology of CRE and Novel Multidrug-Resistant Organisms

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Objectives

- Background on antimicrobial resistance
- Describe CDC Containment Strategy for novel or rare MDROs and available resources
- Describe current landscape for two resistance mechanisms/MDROs targeted by containment strategy
  - Carbapenemases
  - *mcr-1*

Background

Many Different Mechanisms Can Cause Resistance

- Keep antibiotics from getting into the cell
  - Porin modifications
- Pump antibiotics out of the cell
  - Increase activity of efflux pumps
- Inactivate antibiotics or modify antibiotic target
  - Carbapenemases
  - Bacterial cell wall modifications
- Often, a combination of activities contributes to resistance

Location of Resistance Genes is Important

- Chromosomal mutations
  - Can pass resistance vertically but not horizontally
  - Examples include mutations affecting efflux pumps, porins
  - Often incur fitness defect
- Plasmid encoded
  - Can pass resistance vertically and horizontally
  - Examples include Extended Spectrum β-lactamases (ESBLs) and carbapenemases
  - No/minimal fitness defect

Why Are Plasmid-Encoded Mechanisms a Major Threat?

- Potential for swift, epidemic spread
- Can dramatically increase proportion of resistant isolates
- Examples
  - Israel: KPC outbreak
    - 11% carbapenem resistant in 2006
    - 22% carbapenem resistant in 2007
  - Greece: Dissemination of VIM
    - <1% carbapenem resistant in 2001
    - 20%-50% carbapenem resistant in 2006

Schwaber and Carmeli, JAMA. 2008;300(24):2911-2913. doi:10.1001/jama.2008.896
Vatopoulos, EuroSurveillance, Volume 13, Issue 4, 24 January 2008

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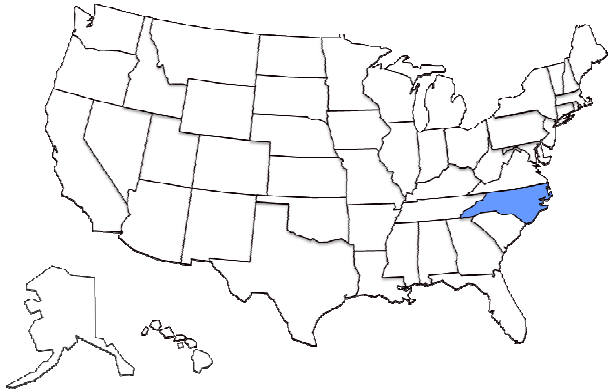
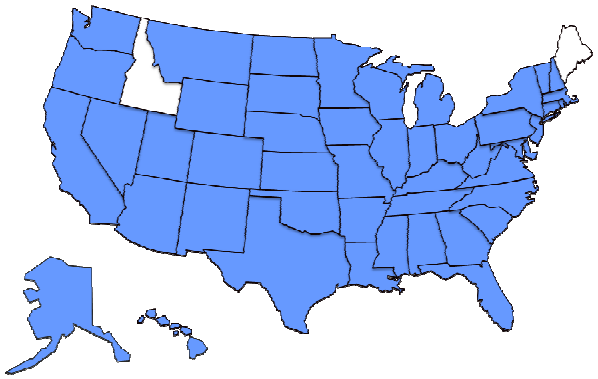
States with KPC-CRE Reported to CDC



2001



2016

Containment

Containment Strategy

- Goal: slow spread of novel or rare multidrug-resistant organisms or mechanisms
- Systematic, aggressive response to single cases of high concern antimicrobial resistance
  - Focus on stopping transmission
- Response activities have tiered approach based on organism/mechanism attributes
- Complements existing guidance
  - CRE Toolkit
  - VRSA Investigation Guide

https://www.cdc.gov/hai/outbreaks/mdro/index.html

Targeted Mechanisms and Organisms by Tier

- **Tier 1**
  - Resistance mechanisms novel to the United States
  - Organisms for which no current treatment options exist (pan-resistant)
  - Organisms and resistance mechanisms for which experience in the United States is extremely limited and a more extensive evaluation might better define the risk for transmission
- Tier 2
- Tier 3

Examples:
Candida auris
VRSA
Pan-Resistant isolates

Response Tiers

- Tier 1
- **Tier 2**
  - MDROs primarily found in healthcare settings but not found regularly in the region
- Tier 3

Examples
mcr-1
CP-CRO (non-KPC)

Response Tiers

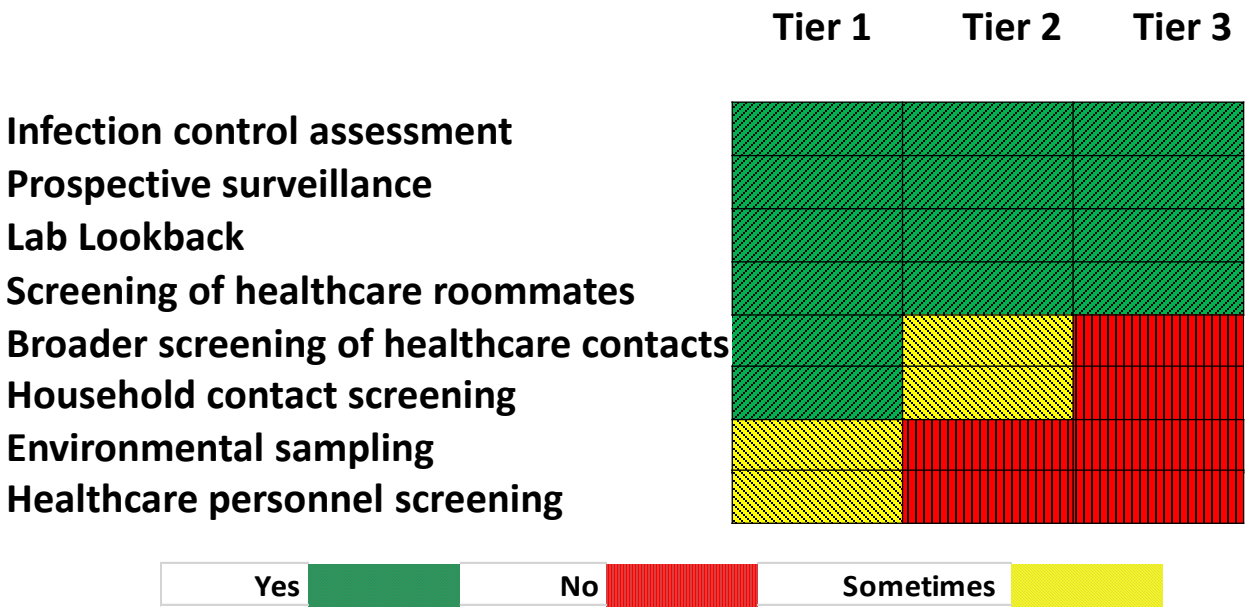
- Tier 1
- Tier 2
- **Tier 3**
  - MDROs targeted by the facility/region that are already established in the United States
  - Uncommon in the region and not thought to be endemic

Example
KPC CRE in many parts of U.S.

Containment Response Elements

Infection control assessment
Prospective surveillance
Lab Lookback
Screening of healthcare roommates
Broader screening of healthcare contact
Household contact screening
Environmental sampling
Healthcare personnel screening

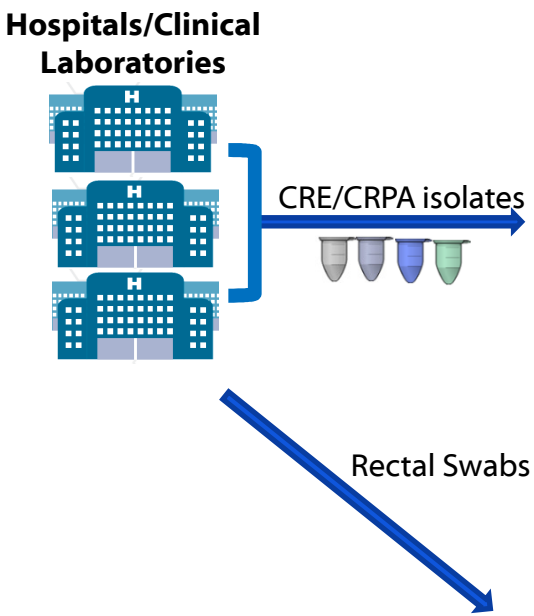
Containment Response Elements



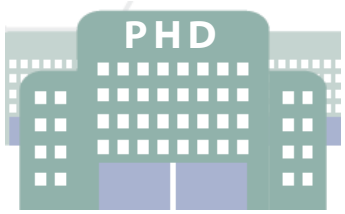
Infection Control Considerations

- Notify patients of their results
- Educate and inform healthcare personnel and visitors
- Ensure adequate PPE and cleaning supplies available and appropriate infection control practices in place
  - hand hygiene
  - transmission-based precautions
  - environmental cleaning
- Flag patient record and ensure patient's status communicated at transfer
- If MDRO present at admission, notify transferring facility
- If transmission identified, further investigation and infection control interventions indicated

Antimicrobial Resistance Laboratory Network (ARLN): Laboratory Support for Containment



Public Health Laboratories
50 States
5 Local Health Departments



Species identification
Confirmatory AST
Phenotypic screening for carbapenemase production
Carbapenemase mechanism testing
mcr-1 testing (some labs)

CRE and CRPA Colonization Screening

Carbapenemase-Producing Organisms

Carbapenemases

- Enzymes that degrade carbapenem antibiotics
- 5 plasmid-encoded enzymes of primary public health concern
  - *K. pneumoniae* carbapenemase (KPC)
  - New Delhi Metallo-β-lactamase (NDM)
  - Verona Integron Mediated Metallo-β-lactamase (VIM)
  - Imipenemase (IMP)
  - OXA-48-type
- Found in Enterobacteriaceae and glucose non-fermenters (e.g., *Pseudomonas aeruginosa* and *Acinetobacter*)

Carbapenem-Resistant Enterobacteriaceae

- NHSN: 3.5% are CRE
- Carbapenemase-production
  - EIP data, 2012-2013: 48% of CRE*
  - ARLN data, 2017: ~33% of CRE
- KPC is most prevalent mechanism in U.S.
  - NDM, OXA-48, VIM, and IMP also identified
- In other countries, different carbapenemases predominate
  - India: NDM
  - Japan: IMP

*Guh et al. JAMA, 2015;314(14):1479-1487.

Carbapenem-Resistant Non-Fermenters

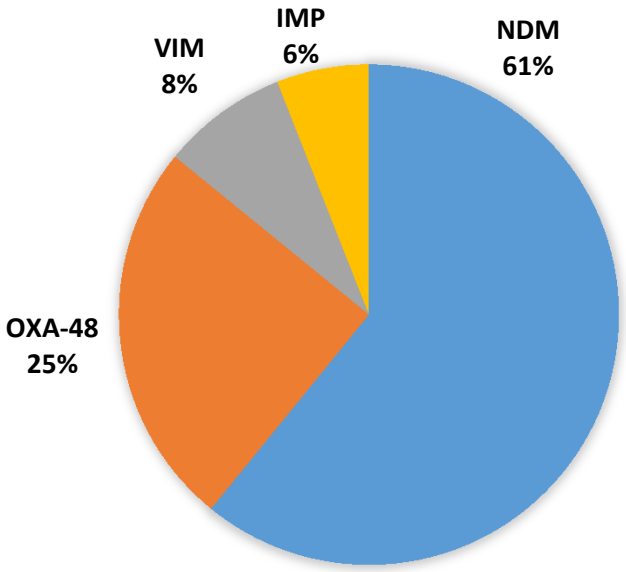
- NHSN: 19% of P. *aeruginosa* and 53% of *Acinetobacter* R to carbapenem
- Sentinel surveillance at 5 US sites in 2015
  - 2% of CRPA tested produced carbapenemase
    - IMP, VIM, and novel enzyme
- Other countries have higher prevalence
  - Brazil 1998-2012: 39% of CRPA produced carbapenemase
  - Europe 2009-2011: 20% of CRPA produced carbapenemase
- VIM is most commonly reported worldwide
  - IMP, KPC, and NDM also reported in U.S

Antibiotic Resistance Patient Safety Atlas: https://gis.cdc.gov/grasp/PSA/
Rizek, C., *Annals of Clinical Microbiology,* 2014, 13: 43
Castanheira, M., *J. Antimicrob Chemother*, 2014, 69: 1804-1014

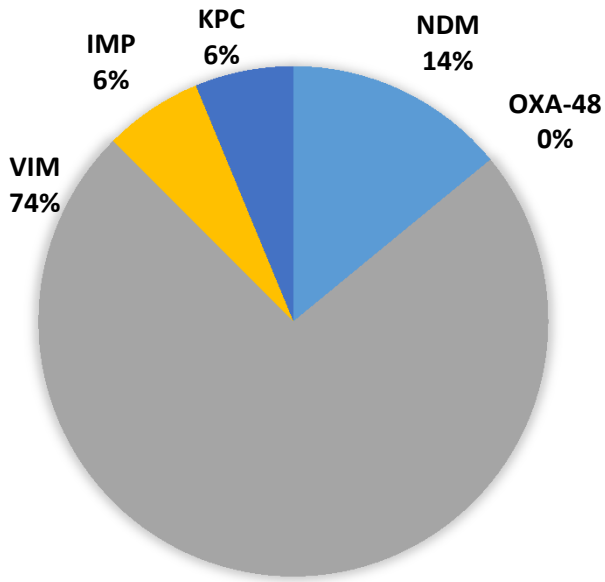
Carbapenemases in Enterobacteriaceae and Non-fermenters reported to CDC, January 1, 2009-April 30, 2017

Non-KPC CP-CRE, N=368

- ~80% of CP-CRE are KPC



CP-Non-fermenters, N=64

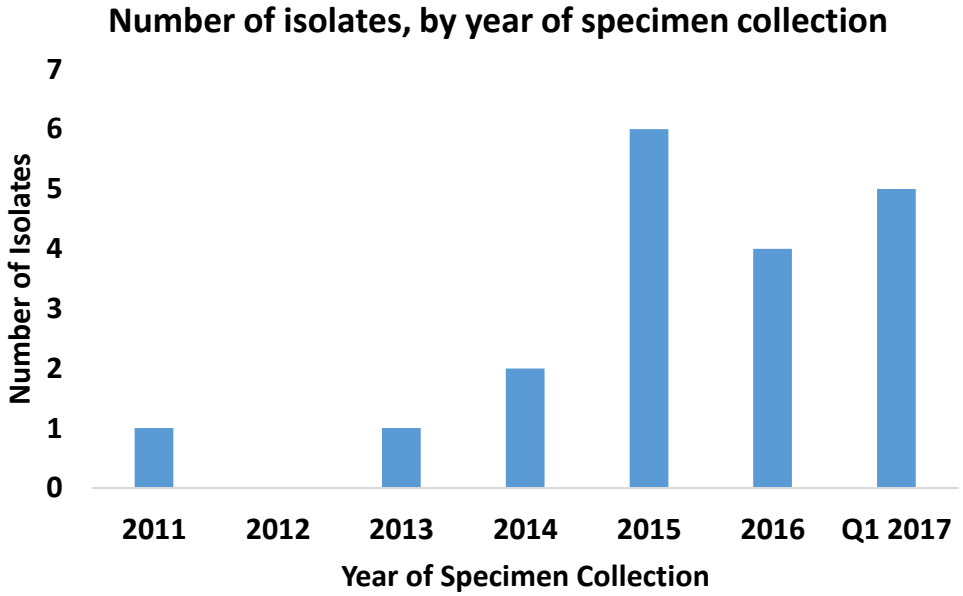


Emerging Issues in Epidemiology of CP-Organisms

#1: Increase of non-KPC carbapenemases reported in Enterobacteriaceae other than *Klebsiella*, *Enterobacter*, and *E. coli*

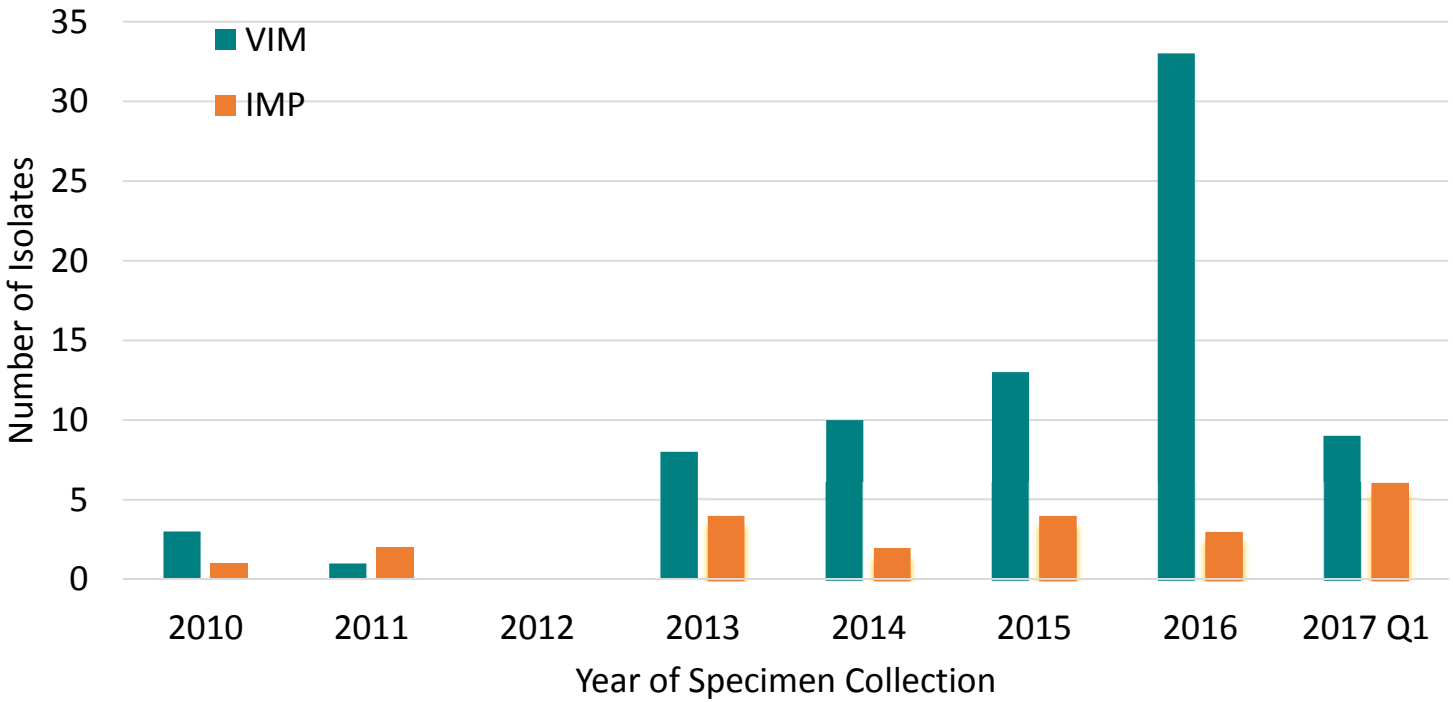
Number of isolates, by organism

Organism	Number of Isolates
Proteus mirabilis	5
Providencia rettgeri	5
Morganella morganii	4
Citrobacter freundii	3
Serratia marcescens	3
Salmonella seftenberg	1
Providencia stuartii	1
Grand Total	**22**



Emerging Issues in Epidemiology of CP-Organisms

#2. Reports of Rare Carbapenemases Increasing



Emerging Issues in Epidemiology of CP-Organisms

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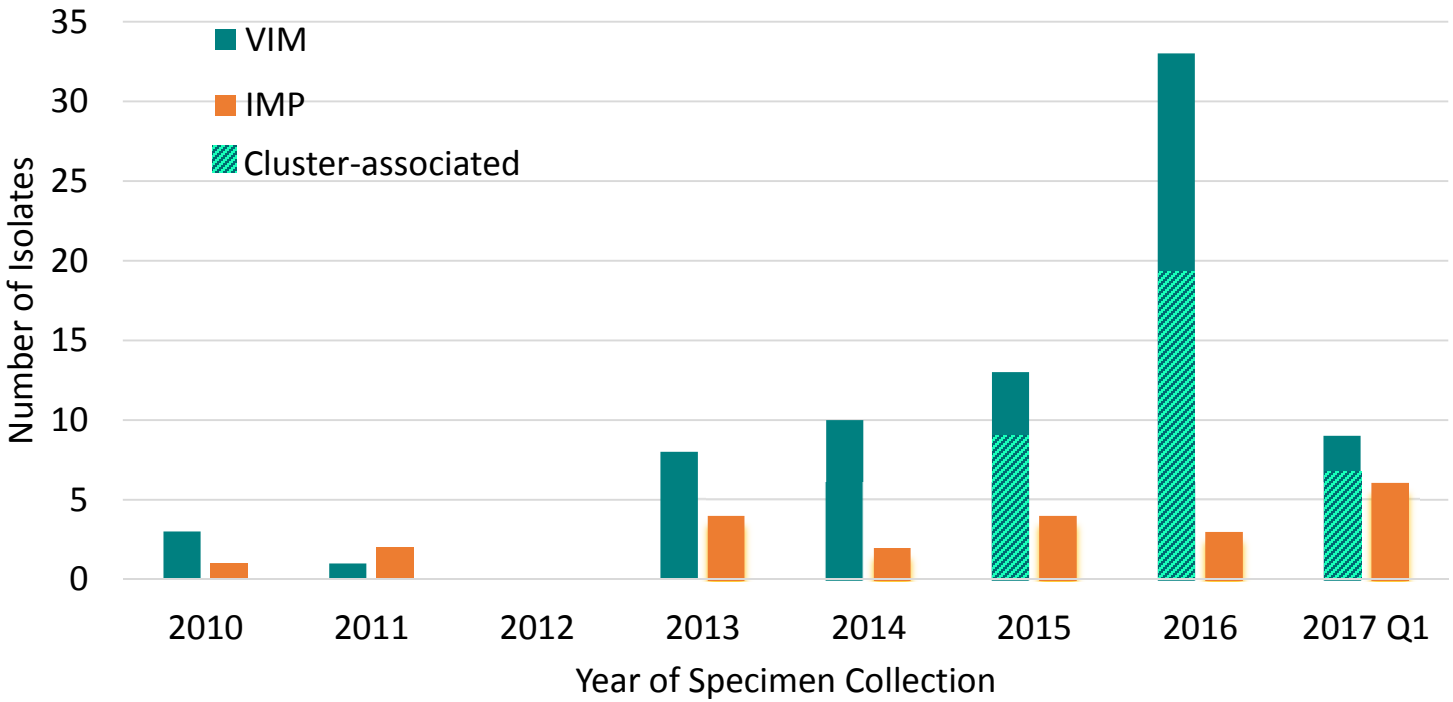


Emerging Issues in Epidemiology of CP-Organisms

#4: CP-CRE in U.S. patients without healthcare or international travel

- EIP CRE surveillance: 13% of all cases are community-associated
- Colorado: 6/10 recent NDM community-associated
  - 2 had recent international travel
- Source currently unknown
  - CP-CRE found in community sources in U.S.
    - OXA-48 in municipal water that failed fecal coliform testing
    - IMP-27 in environmental samples on pig farm
  - Asymptomatic travelers in community
  - Hospital sewage effluent, surface water

What are we learning?

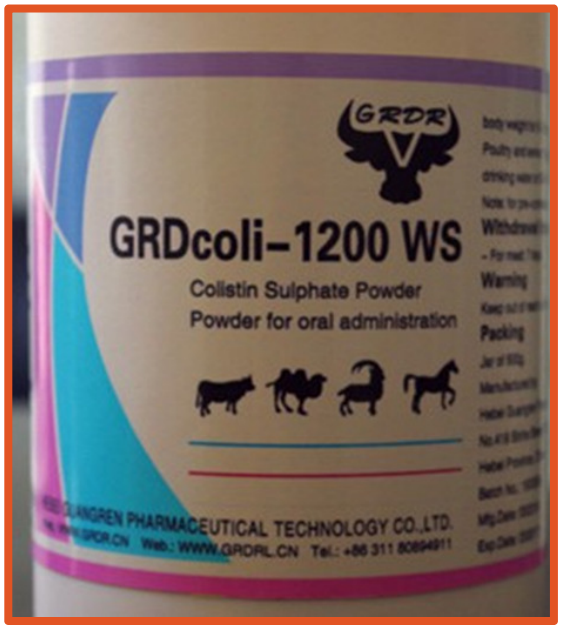
#5: New modes of transmission: sink drains and hoppers

- Hospital sink drains and hoppers can become colonized with CP-CRE and contaminate the patient environment
- Characteristic outbreak “signature”
  - Single mechanism in multiple genus and species
  - Cases persist despite infection control interventions for person to person transmission and environmental cleaning
- Lab work ongoing to describe extent of spread and to evaluate ways to prevent (e.g., lids on hoppers)
- Keep patient supplies away from sink splash zone

Colistin resistance and *mcr-1*

Colistin (polymyxin E)

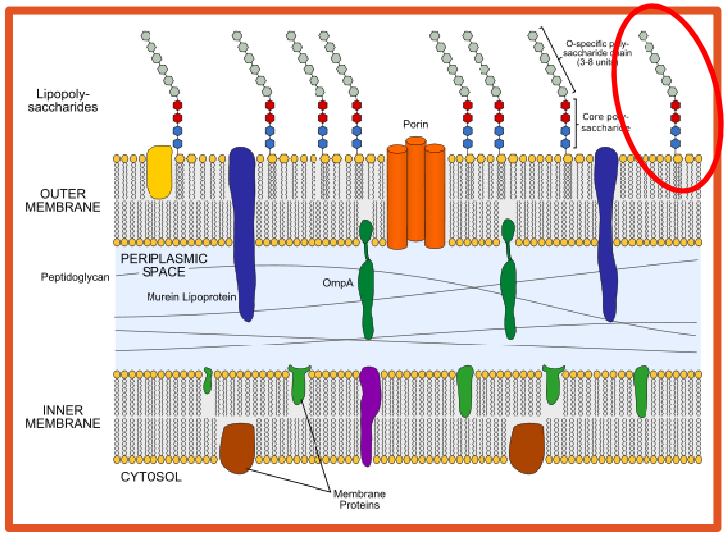
- Polymyxin class of antibiotics
- Antibiotic used to treat serious, highly resistant infections
  - Broad activity against gram negative bacteria
  - Available in U.S. in topical and IV formulations
  - IV use associated with toxicities
  - Used elsewhere orally for selective digestive decontamination
- Used widely in veterinary medicine outside the U.S.



www.alibaba.com

Colistin Resistance

- Chromosomal resistance well-documented
  - Colistin binds lipopolysaccharide
  - Resistance through Lipid A modification
  - ~11% of ESBLs tested at CDC have colistin MIC ≥4 µg/ml
- Plasmid-mediated resistance first reported in November 2015 in China*
  - *mcr-1*: mobile colistin resistance
  - *E. coli* (primarily) and *K. pneumoniae*
  - Meat, animal isolates, clinical isolates



www.bio101.info

*Liu, *Lancet Infet Dis* 2016; 16: 16-68

Colistin Susceptibility Testing

- Multiple methodological issues and technical challenges
  - No FDA-cleared automated testing methods
  - E-test underestimates MIC by 1-2 doubling dilutions
  - Disk diffusion does not work due to poor diffusion
- ASM 2016: Laboratories that choose to test for colistin susceptibilities for clinical decisions should use broth microdilution
  - Vast majority of clinical labs in U.S. do not have this capacity
  - Might need to have reference labs perform this testing

Identifying Isolates for *mcr-1* Screening

- MicroScan ID/AST panel has colistin well (4 µg/ml) for identification
  - Panel accurately identified colistin R in 2 *mcr-1 E. coli* isolates across 3 replicates per isolate and 2 inoculation methods*
  - Could be useful for surveillance purposes for identifying *mcr-1*
  - Cannot be used for clinical purposes
- Gradient diffusion method (e.g. E-test)
  - Issue with false susceptible results (very major errors)
  - Can be only be used for surveillance purposes

*Barbara Zimmer, Beckman Coulter, unpublished data

Global Emergence of *mcr-1*

- Since initial report, found globally
  - >20 countries and 6 continents
  - Food animals, meat, vegetables, surface water
  - Ill patients, asymptomatically colonized patients
- Multiple species: *E. coli, K. pneumoniae, Salmonella enterica, Shigella sonnei*
- Earliest isolates identified from 1980s (chickens, *E. coli*, China)
- Earliest human isolate from 2008 (*Shigella sonnei*, Vietnam)
- Highly transmissible among different bacterial strains
- Increases colistin MICs 8 to 16-fold
  - Typical MICs 4 to 8 µg/ml

Liu, *Lancet Infet Dis* 2016; 16: 16-68
Skov, *Euro Surveill* 2016; 21(9):pii=30155

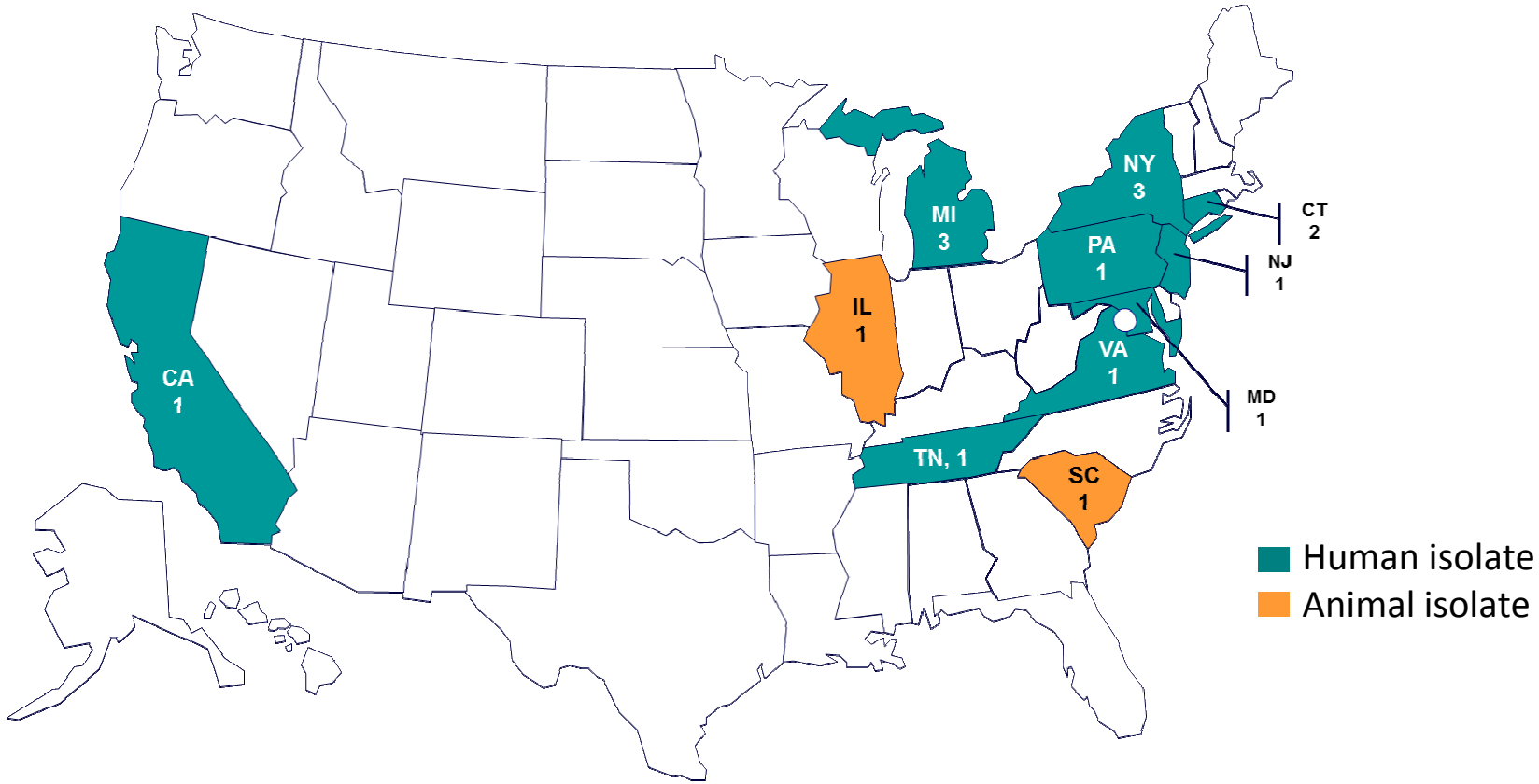
Surveillance for *mcr-1* in the U.S.

- Retrospective surveillance
  - U.S. Government: National Antimicrobial Resistance Monitoring System (NARMS; retail meat, animal, clinical); DHQP reference and surveillance isolates; National Center for Biotechnology Information
  - Academia and private labs: SENTRY, Rutgers
- Prospective surveillance
  - CDC HAN, June 2016: Send Enterobacteriaceae with colistin MIC ≥4 µg/ml to CDC for mechanism testing
  - ARLN: Regional lab testing for *mcr-1*
  - Walter Reed Army Institute of Research MDRO Surveillance Network

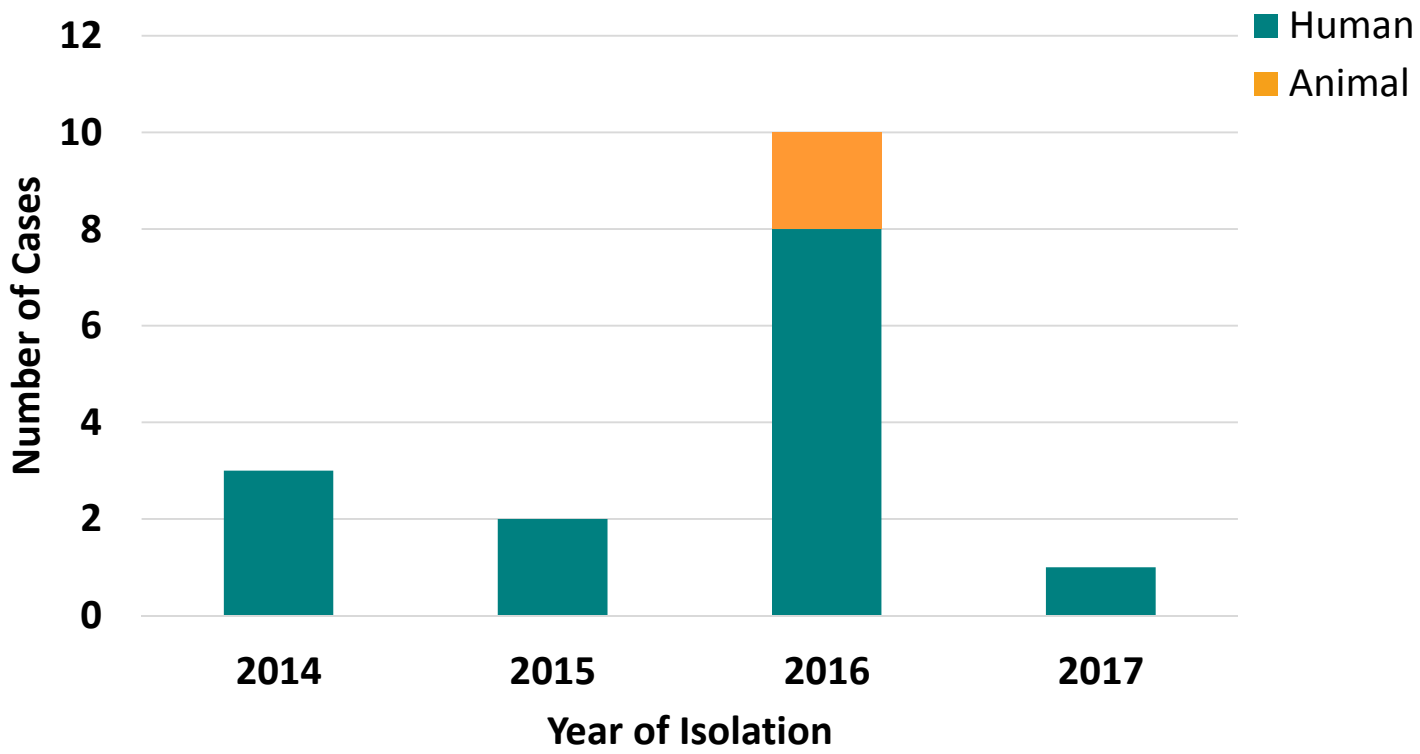
mcr-1 in the U.S.

- 16 reports as of June 1, 2017
  - 14 human isolates (11 *E. coli* and 3 *Salmonella*)
  - 2 porcine isolates collected at slaughter (*E. coli*)
- Primarily ESBLs
  - 1 CP-CRE (NDM)
  - Multiple susceptible to most antibiotics, including 3rd generation cephalosporins

mcr-1 Cases by Location, as of June 1, 2017, n=16



mcr-1 Cases by Year, as of June 1, 2017, n=16



mcr-1 Patient Demographics and Risk Factors

Patient Characteristic	No. of Patients N=14
Median age in years, Range	51 (2-76)
Female	7
Travel outside of U.S. in 6 months prior	10/12
Asia	6
Caribbean	3
Europe	1
Any hospitalization in 6 months prior	6
Hospitalization outside of U.S.	1

mcr-1 Case Study 1: First identification of *mcr-1* in U.S.

- Pennsylvania woman with multiple underlying conditions
- ESBL-*E. coli* isolated from urine collected during outpatient evaluation for urinary tract infection
- Most recent travel: Mexico 10 months prior to specimen collection
- 4 inpatient stays in year prior
  - 2 short stay acute care hospitalizations
  - 5-week inpatient rehabilitation hospitalization
- No animal contact and limited involvement with food preparation
- Multiple household contacts and home visitors who assisted with activities of daily living

Kline, *MMWR* 2016; 65(36); 977-978

mcr-1 Case Study 1: Evaluate for Transmission

- Screening
  - 20/20 high risk contacts: healthcare facility roommate, household contacts, home health personnel
  - 78/98 lower-risk contacts: healthcare personnel who directly assisted with activities of daily living while adhering to contact precautions
  - Point prevalence in 1 of 2 healthcare facilities
  - All 105 contacts screened were negative
  - Index patient screened positive in May and June but negative in August (~4 months after initial culture)
- Prospective surveillance at facilities where patient admitted in 2016
  - 51 ESBL-producing isolates, none colistin resistant

mcr-1 Case Study 2: *Salmonella* with *mcr-1*

- Connecticut woman who traveled to Caribbean on holiday, May 2016
  - Developed diarrhea and vomiting on return trip
  - 3-day hospitalization beginning day after return for pancreatitis
  - Isolate from stool collected in outpatient setting ~1 week after return
    - *mcr-1* identified when sequence uploaded December 2016
  - 2 travel companions, 1 ill
  - 3 household contacts
- *Salmonella* Enteritidis PFGE pattern 2
  - Common PFGE pattern associated with international travel
  - Multistate cluster of >350 cases and CT cluster of 20 cases

mcr-1 Case Study 2: *Salmonella* with *mcr-1*

- Screening
  - 2 household contacts and 2 travel companions
  - Re-swabbed index patient
  - All negative for *mcr-1* and *Salmonella*
  - Did not screen roommate (overlap 4 hours)
- *Salmonella* Enteritidis pattern 2
  - Looked for *mcr-1* in >100 isolates from clusters
  - Evaluated *Salmonella* from acute care hospital for *mcr-1*
  - All negative
- No colistin susceptibility testing done at hospital clinical lab

Key Findings from *mcr-1* Investigations

- Most cases associated with travel, likely community-acquired
- Majority of isolates *E. coli*
  - Only one CP-CRE
- No transmission identified
- Generally limited duration of intestinal colonization, but concern for persistent colonization in urine
- Isolates will continue to be identified through ongoing surveillance efforts
  - Report isolates to public health and to clinicians caring for patient
  - Continue to gather epi and do contact tracing for each case
  - Focus on preventing transmission, particularly in healthcare settings

Summary

Summary

- Multiple MDROs are targeted by containment strategy
  - Identify and isolate
  - Infection control interventions
  - Identify transmission
- In addition to slowing spread, containment activities are providing new epi information that can be used to adapt strategy
- Successful containment requires collaboration among many players
  - CDC, State and local health departments, facilities across the continuum of care, clinical and public health laboratories
  - Information you share with Brenda and Sara when patients with targeted MDROs are identified can help slow spread of these MDROs

Thank you

Contact:
MSWalters@cdc.gov

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov